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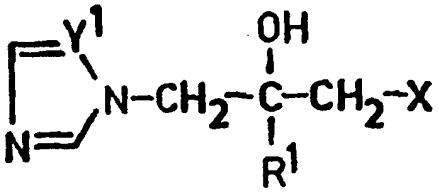
(54) Title: NOVEL SUBSTITUTED PROPANE-2-OL DERIVATIVES

(57) Abstract

The invention relates to novel substituted propane-2-ol derivatives of formula (I), wherein R^1 represents a C_{1-10}alkyl group, a phenyl group or a phenyl-C_{1-6}alkyl group, and the phenyl moiety of the two latter groups may carry at least one substituent selected from the group consisting of a halogen atom, C_{1-6}alkoxy group, phenyl group, phenoxy group and trifluoromethyl group; X represents a hydrogen or halogen atom; and Y^1 represents a -N= atom or a group of the formula --CH=, and optical antipodes and racemates thereof, further to pharmaceutical compositions of fungicidal action, containing such compounds, processes for the preparation of these compounds and compositions, finally to a method of treatment by using these compounds and compositions.



(I)

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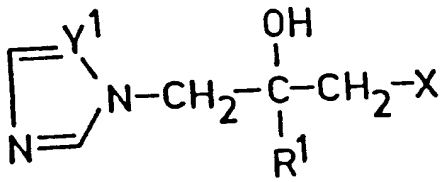
NOVEL SUBSTITUTED PROPANE-2-OL DERIVATIVES

The invention relates to novel substituted propane-2-ol derivatives, optical antipodes and racemates thereof, fungicidal compositions containing such compounds as well as to processes for preparing such compounds and compositions. Furthermore, the invention relates to a method of treating diseases caused by fungi, said method comprises administering one or more of the compounds of the present invention in a fungicidally effective amount to a mammal, including men, by using a compound of the invention per se or in the form of a pharmaceutical composition.

The compounds of the present invention are characterized by the formula (I)



(I),

wherein

R^1 represents a C_{1-10}alkyl group, a phenyl group or a phenyl-C_{1-6}alkyl group, and the phenyl moiety of the two latter groups may carry at least one substituent selected from the group consisting of a halogen atom, C_{1-6}alkoxy group, phenyl group, phenoxy group and trifluoromethyl group;

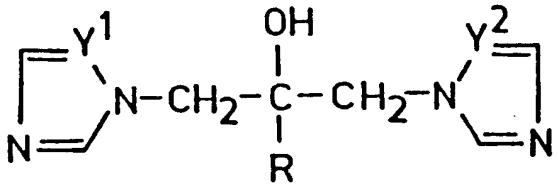
X represents a hydrogen or halogen atom; and

Y^1 represents a -N= atom or a group of the formula -CH=.

The compounds of the formula (I) may exist in the form of optical antipodes. A 1:1 mixture of the antipodes forms

a racemic mixture. If there is no hint to an individual antipode, it is self-evident that all the possible three forms are comprised by a reference to a compound of the formula (I). During the preparation process of the compounds of the formula (I) a racemic mixture thereof is formed. From this mixture the individual antipodes can be separated in a manner known per se, e.g. by selective crystallization of a diastereomeric salt pair formed with an optically active compound and then by deliberalization of the optically active compound of the formula (I).

GB patent specification No. 2,078,719 A relates to highly effective fungicidal compounds, possessing substantial plant growth regulating effect, too. These compounds are characterized by formula



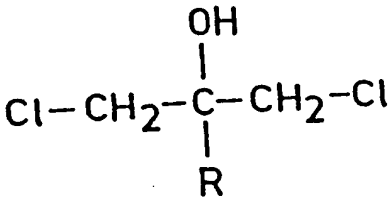
(A)

if R represents an alkyl, cycloalkyl, aryl or aralkyl, all these groups being optionally substituted by one or two halogen(s), or said aryl or aralkyl groups may carry alkoxy, phenyl, phenoxy or trifluoromethyl substituents; Y^1 is as defined above; and Y^2 represents a -N= atom or a group of the formula -CH=, being thus identical to or different from Y^1.

According to the GB patent specification No. 2,099,818 A 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propane-2-ol is used as a highly effective human fungicide. It is sold in the form of a human fungicidal pharmaceutical under the trade name fluconasole or diflucane.

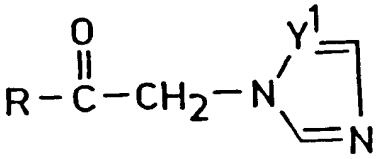
In accordance with the GB patent specification No. 2,078,719 A the propane-2-ol derivatives of the formula (A) can be prepared by reacting a Grignard reagent of the

formula R-Mg-halogen with dichloroacetone. The thus-obtained 1,3-dichloropropane-2-ol derivative of the formula



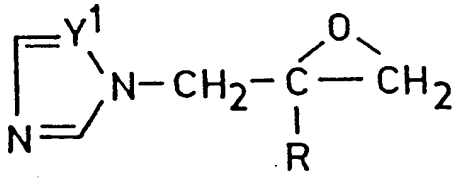
(III)

is reacted with an imidazole or triazole salt, e.g. sodium salt, taken in an excess, in the presence of a protic or aprotic solvent, e.g. dimethyl formamide. The reaction can be carried out with epoxi derivatives being prepared <u>in situ</u> through elimination of hydrogen chloride from the dihalogen compound with a base. The target compounds can be prepared by reacting the corresponding 1,3-bisimidazolyl or 1,3-bis(1,2,4-triazol-1-yl)acetone and a Grignard reagent of the formula R-Mg-halogen, too. According to a further preparation method a compound of the formula



(IV)

is reacted with dimethyloxosulphoniummethylide, then a thus-obtained compound of the formula



(V)

is reacted, similarly to the process described above, with the sodium salt of imidazole or triazole. The starting materials of the above processes can be prepared by known methods.

The process for the preparation of the active ingredient of Fluconasole according to GB patent specification No. 2,099,818 A comprises the reaction of compounds of the formulae (III) and (V), too but instead of 1,2,4-triazol-1-yl sodium a base and triazole are used.

A common feature of the processes described in the GB patent specifications Nos. 2,078,719 A and 2,099,818 A resides in that when isolating the target compounds the reaction mixture is first diluted with water, then extracted and the product is isolated and purified by known methods like column chromatography or fractioning in vacuo, etc. The yields amount to about 30-50%.

In accordance with the GB patent specification No. 2,078,719 A the esters and ethers of the target alcohols can be prepared by reacting the salt of the alcohol, formed with sodium hydride, with a corresponding acylating or alkylating agent.

According to the ES patent specification No. 549,020 A1 one mole of 1,3-dichloroacetone is reacted with 2 moles of 1,2,4-triazole, then the 1,3-bis(1,2,4-triazol-1-yl)-propane-2-on, obtained with a very low yield, is reacted with 2,4-difluorophenyl magnesium bromide to give the active ingredient of fluconasole. Based on the Grignard reagent the yield amounts to about 45%.

The common feature of the ES patent specifications Nos 549,021 A1, 549,022 A1 and 549 684 A1 is that one or both of the triazolyl moieties of 2-(2,4-difluorophenyl)-1,3-bis(1,2,4-triazol-1-yl)propane-2-ol is or are introduced by using a (1,2,4-triazol-1-yl)methyl magnesium halogenide. According to these specifications the yield amounts to about 45-55%. It is well known that the Grignard reagents containing a triazolyl group are unstable resp. sometimes inactive, therefore they can be reacted with a bad efficiency. When reproducing the processes of these

patent specifications the yield was every time below 10%.

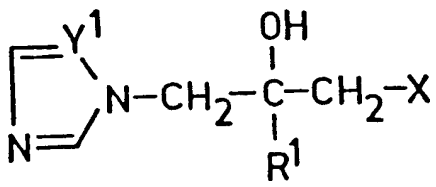
The ES patent specification No. 2,026,416 describes a process being more preferable than the above described processes. Thus, a 1-(1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-halopropane-2-ol is reacted with 4-amino-1,2,4-triazole, then the obtained 1-(1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-3-(4-amino-1,2,4-triazol-1-yl)propane-2-ol is diazoted in order to remove the amino group and the obtained diazonium salt is decomposed. As the yield of these steps 78%, resp. 85% are given. From an industrial viewpoint this process possesses several disadvantages. The first one is that in order to obtain a 3-halopropane-2-ol derivative used as starting material an epoxide derivative corresponding to the formula (V) has to be heated in a very corrosive medium comprising a hydrogen halide. A further disadvantage is that the reagent 4-amino-1,2,4-triazole is hardly available, it is commercialized only as a fine chemical. The diazotation and the decomposition of the diazonium salt are, on an industrial scale, very dangerous steps. Finally, the total yield of the very cumbersome process of several steps is as few as 42-43%.

During tests carried out with the active ingredient of fluconasole, used in a high volume in view of its very substantial human fungicidal action of wide spectrum, it was established that said active ingredient has a relatively weak effect against the very wide-spread pathogenic fungus Candida albicans. Mainly this resistant species causes the disease called "candidiasis" which is quite wide-spread and very difficult to influence. According to our in vitro tests the active ingredient of fluconasole ensures a full inhibition against other Candida species and other pathogenic fungi in a very low dose, i.e. 0.1 to 10 μg/ml; however, in the case of Candida albicans this

inhibiting effect occurs only at a dose of 2500 μg/ml.

During our research work with the purpose of obtaining fungidical agents of increased effect with broader spectrum it was surprisingly recognized that the propane-2-ol derivatives of the formula (I) possess a surprisingly high fungicidal action of broad spectrum, that is, in addition to plant fungi they are effective mainly against human fungus strains.

Thus, the first object of the present invention relates to propane-2-ol derivatives of the formula (I)



(I),

wherein

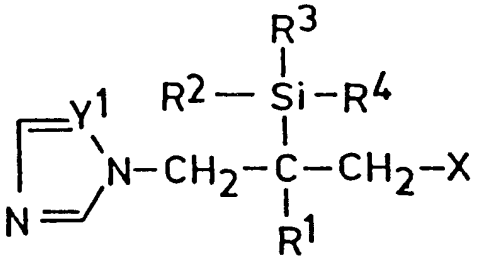
R^1 represents a C_{1-10}alkyl group, a phenyl group or a phenyl-C_{1-6}alkyl group, and the phenyl moiety of the two latter groups may carry at least one substituent selected from the group consisting of a halogen atom, C_{1-6}alkoxy group, phenyl group, phenoxy group and trifluoromethyl group;

X represents a hydrogen or halogen atom; and

Y^1 represents a -N= atom or a group of the formula —CH=,

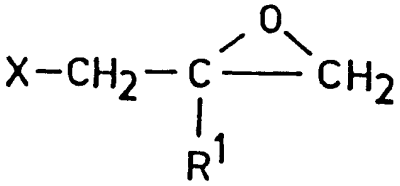
and optical antipodes and racemates thereof.

Further, it was recognized that the propane-2-ol derivatives of the formula (I) can be prepared with a quantitative yield through the hydrolysis of a silyl ether of the formula



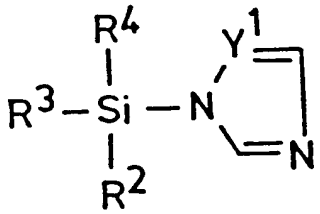
(II),

in a strongly acidic or basic aqueous medium, said silyl ether of the formula (II) is being prepared, for example, by reacting an epoxide derivative of the formula



(VI)

with a silyl triazole resp. silyl imidazole derivative of the formula



(VII)

in the presence of a strongly basic catalyst.

Thus, the second object of the present invention is a process for the preparation of the propane-2-ol derivatives of the formula (I) and optical antipodes and racemates thereof. This process is characterized by

hydrolizing a silyl ether of the formula (II), wherein R^1, X and Y^1 are as defined above, R^2 represents a hydrogen atom, a C_{1-10}alkyl group or a phenyl group, R^3 and R^4 are, independently from each other, a C_{1-10}alkyl or phenyl group, in an aqueous solution having a pH value of lower than 3 or higher than 8,

and, if desired, resolving a compound of the formula (I) obtained in the form of a racemate.

The hydrolysis proceeds quickly. The trimethyl silyl

ethers can be fully hydrolized within 10 minutes at room temperature in a mixture of 10% by volume of water and 90% by volume of dimethyl formamide, said mixture having a pH value over 10. In the same medium and at the same temperature but at a pH value below 2 the hydrolysis proceeds within 0,5-1 hour.

The hydrolysis is suitably performed in a homogeneous phase, in the mixture of a water-miscible protic or aprotic dipolar solvent and water at a pH value falling into the above-identified range.

The isolation of the target compounds of the formula (I) is suitably performed by diluting the reaction mixture with water and cooling the thus-obtained aqueous mixture. The target compounds are separating in a high purity and can be isolated e.g. through filtration.

The hydrolysis according to the present invention can be also performed in such a manner that the silyl ethers of the formula (II) used as starting materials are not separated from the reaction mixture of their preparation but rather about 5% by volume of water is added to this reaction mixture and the obtained aqueous mixture is mixed. In this case the basic catalyst used at the preparation of the silyl ether derivatives of the formula (II) ensures a pH value higher than 8, needed to the hydrolysis. After the hydrolysis is complete, a part of the organic solvent being present in the reaction mixture is, if desired, removed, then the remaining mixture is diluted with water. Under cooling the target compounds of the formula (I) separate and can be isolated e.g. through filtration.

If one uses an optically active compound of the formula (II) as starting material, mostly a corresponding optically active target compound of the formula (I) is obtained. The racemic mixtures of the compounds of the

formula (I) can be separated to their components by known methods, e.g. by selective crystallization of a diastereomeric salt pair formed with an optically active acid and deliberating the compound of the formula (I) from said salt.

The compounds of the formula (VI) used as starting materials for the preparation of the compounds of the formula (II) are either known compounds or can be prepared by known methods. By reacting the compounds of the formula (VI) with compounds of the formula (VII) the starting materials of the process of the invention, i.e. the compounds of the formula (II), can be obtained. To the silylation as a compound of the formula (VII) trimethyl silyl derivatives obtained from the easily available trimethylchlorosilane and imidazole resp. triazole are used.

The fungicidal action of the compounds of the formula (I) was examined in the following in vitro tests.

Densitometric measurement of the propagation of yeast fungi

A microbiological analysator called BIOSCREEN C (LABSYSTEMS, Helsinki, Finland) was used to the measurements. From the test compounds first a stock solution of a concentration of 50 mg/ml, then in 15 steps a bisecting dilution series was prepared with dimethyl sulfoxide. From every dilution step 10 µl each was introduced into the cells of the analysator. Then 390 µl of an aqueous nutrient solution was pipetted into the cells. In the mixtures obtained the cells of the yeasts, e.g. Candida albicans, were suspended in such an amount that the optical density of the suspension obtained be about 0,1. Young cultures, shaken at 30°C for about 12 hours, were used to the preparation of the suspensions. The composi-

tion of the aqueous nutrient solution was as follows: 1 5 by weight of glucose, 0.5% by weight of yeast extract (a product of the firm OXOID Ltd, Great Britain, under the catalogue No. L21) and 0.5% by weight of nutrient broth (a product of the firm OXOID Ltd, Great Britain, under the catalogue No. CM 1/2). The concentration of the compounds to be tested in the cells corresponded to 1250, 625, 312, 156, 78, 39, 19, 9, 4, 2, 1, 0.6, 0.3, 0.15 and 0.07 μg/ml, resp. The densitometric measurement of the cultures was carried out during an incubation at 37°C for 30 hours. The change in the turbidity of the culture, which can be followed through optical measurement, is proportional to the propagation of the yeast fungi.

As the minimal inhibitory concentration (MIC) of this test that minimal concentration of the tested compound was determined which was able to prevent totally the propagation of the fungus. The obtained results are given in the following Table.

Table

MIC values [μg/ml] of the individual tests

Active agent	Candida albicans
compound of Example 5	625
compound of Example 6	19
compound of Example 7	150
fluconasole	2500

Thus, the third object of the present invention is a method of treating fungicidal infections of mammals, including men. This method is characterized by administering a fungicidally effective amount of one or more of the novel propane-2-ol derivatives of the formula (I) or an optical antipode or racemate thereof to said mammal, optionally together with a pharmaceutically acceptable carrier and/or other adjuvant.

The therapeutic use of the compounds of the formula

(I) is suitable in the case of all the diseases where the main aim is the control of a pathogenic fungus being already present in the organism. The compounds of the present invention can be used both in the human and veterinary therapies. During such therapies the daily oral or parenteral dose of the compounds of the formula (I) is about 0.1 to 10 mg/kg, by administering said dose at once or in divided subdoses.

The fourth object of the present invention relates to pharmaceutical compositions of fungicidal action. These compositions are characterized by containing a fungicidally effective amount of one or more of the compounds of the formula (I) or an optical antipode or racemate, together with a pharmaceutically acceptable carrier and/or other adjuvant.

These pharmaceutical compositions are prepared by known methods and are suitable for parenteral or enteral use. The carriers may be non-toxic inert solid or liquid carriers like water, gelatine, milk sugar, starch, pectine, magnesium stearate, talc and vegetal oils.

These pharmaceutical compositions can be prepared in the usual forms, mainly in solid forms, like rounded-off or angular tablets, dragées, capsules (e.g. gelatine capsules), pilules and suppositories.

Based on one tablet the amount of the solid active agent may vary in a wide range, preferably between 25 mg and 1 g. In addition to the carriers these pharmaceutical compositions may contain usual pharmaceutical additives like conserving agents.

The pharmaceutical compositions of the invention can be prepared by known methods, like in the case of solid compositions through sieving, mixing, granulating and optionally pressing the components. The thus-obtained compositions may be subjected to usual pharmaceutical post-

treatments like to sterilisation in the case of injections.

The present invention is elucidated by the aid of the following non-limiting examples.

Example 1

1,2-Epoxy-2-(2,4-difluorophenyl)-3-chloropropane

32.5 g (0.135 moles) of 2-(2,4-difluorophenyl)-1,3-dichloropropane-2-ol, prepared by a method described in the GB patent specification No. 2,978,719 A, is dissolved in 200 ml of dichloromethane, then at room temperature a solution of 8 g (0.2 moles) of sodium hydroxide in 40 ml of water and 1 ml of a 40% aqueous solution of tetrabutyl ammonium hydroxide are added. The reaction mixture is mixed for half hour at room temperature, then the organic phase is separated, washed twice with 50 ml of water each and once with 50 ml of saturated aqueous sodium chloride solution, dried over water-free magnesium sulphate, filtered, washed with twice with 5 ml of dichloro methane each and the solvent is evaporated. 26 g (93.7%) of the title compound as a light yellow oil are obtained; $n^{20}D$ = 1.4978.

Example 2

1,2-Epoxy-2-(2,4-difluorophenyl)propane

One proceeds as in Example 1 but 27.88 g (0.135 moles) of 2-(2,4-difluorophenyl)-1-chloro-propane-2-ol, prepared by a method described in the GB patent specification No. 2,978,719 A, is used instead of 2-(2,4-difluorophenyl)-1,3-dichloropropane-2-ol. 20.7 g (90.2%) of the title compound as a light yellow oil are obtained; $n^{25}D$ = 1.5264.

Example 3

2-(2,4-Difluorophenyl)-1-chloro-3-(1,2,4-triazol-1-yl)-2-(trimethylsilyloxy)propane

4.11 g (0.02 moles) of 1,2-epoxy-2-(2,4-difluorophenyl)-3-chloropropane are reacted with 4.23 g (0.03

moles) of 1-(trimethylsilyl)-1,2,4-triazole and 0.1 g (0.001 mole) of 1,2,4-triazol-1-yl potassium in 50 ml of dimethyl formamide at 50°C for 2 hours. Then the reaction mixture is neutralized by glacial acetic acid, mixed with 250 ml of water at room temperature and extracted twice with 50 ml of dichloromethane each. The united extracts are washed three times with 50 ml of water each, dried over water-free sodium sulphate and evaporated in vacuo. The residue is subjected to column chromatography by using the filling material "Kieselgel 40" of the firm MERCK with a particle size of 70-230 mesh and a 20:1 mixture of ethyl acetate and methyl alcohol as eluting agent. The pure fractions are mixed together and evaporated to free of solvents. The evaporating residue is crystallized from n-heptane. 4.9 g (71.5%) of the title compound are obtained; m.p.: 59-61°C.

Example 4

2-(2,4-Difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-(trimethylsilyloxy)propane

5.13 g (0.03 moles) of 1,2-epoxy-2-(2,4-difluorophenyl)-propane are reacted with 6.35 g (0.045 moles) of 1-(trimethylsilyl)-1,2,4-triazole and 0.14 g (0.0015 moles) of 1,2,4-triazol-1-yl sodium in 40 ml of dimethyl formamide at 80°C for 3 hours. Then the reaction mixture is cooled to room temperature, neutralized by glacial acetic acid, mixed with 200 ml of water and extracted twice with 50 ml of dichloro methane each. The united extracts are washed three times with 50 ml of water each, dried over water-free sodium sulphate and evaporated in vacuo. After carrying out a separation, removal of the solvent and crystallization from n-heptane as described in Example 3 6.0 g (64.5%) of the title compound are obtained; m.p.: 51-53°C.

The other starting compounds of the formula (II) can

be prepared by the methods disclosed in the above Examples 1 to 4.

Example 5

2-(2,4-Difluorophenyl)-3-(1,2,4-triazol-1-yl)-propane-2-ol

6.22 g (0.02 moles) of 2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-2-(trimethylsilyloxy)propane in a mixture of 30 ml of methanol and 2 ml of water are mixed at room temperature for 1 hour in the presence of 0,06 g (0.015 moles) of sodium hydroxide. Then 300 ml of water are added and the obtained mixture is cooled to 0°C. The separated material is filtered off and dried. 4.54 g (95%) of the title compound are obtained; m.p.: 84-85°C.

Example 6

1-Chloro-2-(2,4-difluorophenyl)-3-(imidazol-1-yl)propane-2-ol

3.44 g (0.01 mole) of 1-chloro-2-(2,4-difluorophenyl)-3-(imidazol-1-yl)-2-(trimethylsilyloxy)propane in a mixture of 18 ml of methanol and 2 ml of water are mixed at room temperature for 1 hour in the presence of 0,04 g (1 mmole) of sodium hydroxide. The reaction mixture is evaporated to a volume of 6 ml and 50 ml of water are added. The separated material is filtered off at 0°C. 2.4 g (88%) of the title compound are obtained; m.p.: 142-144°C.

Example 7

1-Chloro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-propane-2-ol

3.45 g (0.01 mole) of 2-(2,4-difluorophenyl)-1-chloro-3-(1,2,4-triazol-1-yl)-2-(trimethylsilyloxy)propane in a mixture of 20 ml of ethyl alcohol, 20 ml of water and 0.1 ml of concentrated hydrochloric acid are mixed at room temperature for 1 hour, then made free of solvents through destillation. 10 ml of water and 20 ml of dichloromethane are added to the residue and pH value of the obtained mix-

ture is adjusted to 8 by using a 10% sodium hydroxide solution. The organic phase is dried over water-free sodium sulphate and evaporated. The residue is crystallized from n-hexane. 2.54 g (93%) of the title compound are obtained; m.p.: 67-69°C.

Example 8

1-Chloro-2-(2,4-difluorophenyl)-3-(imidazol-1-yl)propane-2-ol

4.11 g (0.02 moles) of 1,2-epoxi-3-chloro-2-(2,4-difluorophenyl)propane are reacted with 4.20 g (0.03 moles) of 1-(trimethylsilyl)imidazole and 0.09 g (1 mmole) of imidazol-1-yl sodium in 40 ml of dimethyl formamide at 60°C for 2 hours, then 0,5 ml of water are added, the mixing is continued at 30°C for a further half hour and finally the reaction mixture is evaporated in vacuo. The residue is subjected to partition between 80 ml of water and 60 ml of dichloromethane, the organic phase is separated and subjected to chromatography as disclosed in Example 3. 3.61 g (66%) of the title compound are obtained; m.p.: 142-144°C.

Example 9

Tablets of a weight of 100 mg, containing 10 mg of active ingredient

50.0 g of active ingredient,
285.0 g of lactose,
100.0 g of potato starch,
2.5 g of sodium dodecyl sulphate,
5.0 g of polyvinylpyrrolidone (Kollidon-K 90^R),
50.0 g of microcrystalline cellulose (Avicel^R) and
7.5 g of vegetable oil (Sterotex^R)

are compressed in a known manner to tablets of a weight of 100 g by wet granulating and pressing. Each of these tablets contains 10 mg of active ingredient.

Example 10

Dragées of a weight of 125 mg, containing 10 mg of active ingredient

The tablets prepared in accordance with the method of Example 9 are covered in a known manner with a covering comprising sugar and talc. Finally, they are polished with a mixture of beewax and carnaubawax.

Example 11

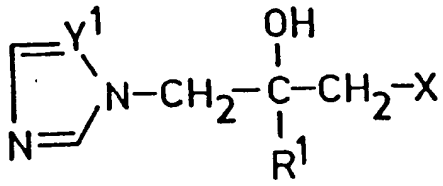
Capsules containing 20 mg of active ingredient

40.0 g of active ingredient,
12.0 g of sodium lauryl sulphate,
102.0 g of lactose,
102.0 g of potato starch,
2.4 g of magnesium stearate, and
1.6 g of colloid silicon dioxide

are thoroughly mixed together and the obtained mixture is filled into hard gelatine capsules, containing 20 mg of active ingredient each.

What we claim is:

1. A novel propane-2-ol derivative of the formula (I)



(I),

wherein

R^1 represents a C_{1-10}alkyl group, a phenyl group or a phenyl-C_{1-6}alkyl group, and the phenyl moiety of the two latter groups may carry at least one substituent selected from the group consisting of a halogen atom, C_{1-6}alkoxy group, phenyl group, phenoxy group and trifluoromethyl group;

X represents a hydrogen or halogen atom; and

Y^1 represents a -N= atom or a group of the formula -CH=,

and optical antipodes and racemates thereof.

2. 2-(2,4-Difluorophenyl)-3-(1,2,4-triazol-1-yl)-propane-2-ol.

3. 1-Chloro-2-(2,4-difluorophenyl)-3-(imidazol-1-yl)propane-2-ol.

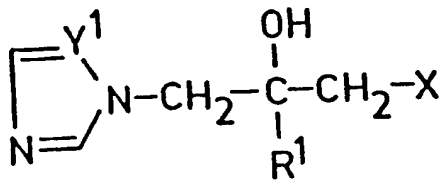
4. 1-Chloro-2-(2,4-difluorophenyl)-3-(1,2,4-triazol-1-yl)-propane-2-ol.

5. A pharmaceutical composition of fungicidal action characterized by containing a fungicidally effective amount of one or more of the novel propane-2-ole derivative of the formula (I), wherein R^1, X and Y^1 are as defined in claim 1, or an optical antipode or racemate thereof, together with a pharmaceutically acceptable carrier and/or other adjuvant.

6. A method of treating fungicidal infections of

mammals, including men, characterized by administering a fungicidally effective amount of one or more of the novel propane-2-ol derivatives of the formula (I) , wherein R^1, X and Y^1 are as defined in claim 1, or an optical antipode or racemate thereof to said mammal, alone or in the form of a pharmaceutical composition.

7. A process for the preparation of propane-2-ol derivatives of the formula



(I),

wherein

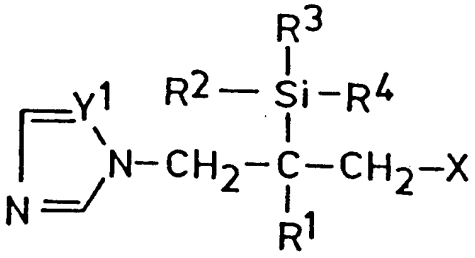
R^1 represents a C_{1-10}alkyl group, a phenyl group or a phenyl-C_{1-6}alkyl group, and the phenyl moiety of the two latter groups may carry at least one substituent selected from the group consisting of a halogen atom, C_{1-6}alkoxy group, phenyl group, phenoxy group and trifluoromethyl group;

X represents a hydrogen or halogen atom; and

Y^1 represents a -N= atom or a group of the formula -CH=,

and optical antipodes and racemates thereof, characterized by

hydrolizing a silyl ether of the formula



(II),

wherein R^1, X and Y^1 are as defined above, R^2 represents a hydrogen atom, a C_{1-10}alkyl group or a phenyl group, R^3 and R^4 are, independently from each other, a C_{1-10}alkyl or phenyl group, in an aqueous solution having a pH value of lower than 3 or higher than 8,

and, if desired, resolving a compound of the formula (I) obtained in the form of a racemate.

8. A process as claimed in claim 7, characterized by carrying out the hydrolysis in a mixture of water and dimethyl formamide in the presence of sodium hydroxide.

9. A process as claimed in claim 7, characterized by carrying out the hydrolysis in a mixture of water and methyl alcohol in the presence of potassium hydroxide.

10. A process as claimed in claim 7, characterized by carrying out the hydrolysis without separating the compound of the formula (II), wherein R^1, R^2, R^3, R^4, X and Y^1 are as defined in claim 7, from the reaction mixture used for its preparation, through adding water to this mixture.

11. A process for the preparation of pharmaceutical compositions having pharmaceutical action, characterized by admixing one or more of the compounds of the formula (I), wherein R^1, X and Y^1 are as defined in claim 1, or optical antipodes or racemates thereof to a pharmaceutically acceptable carrier and/or other adjuvant and converting the mixture obtained to a pharmaceutical composition in a known manner.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00039

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6]: C 07 D 249/08, 233/60; A 61 K 31/41, 31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6]: C 07 D 249/08, 233/60; A 61 K 31/41, 31/415

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

DARC (Questel)

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[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 November 1994 (15.11.94)	12 December 1994 (12.12.94)
Name and mailing address of the ISA/ AT AUSTRIAN PATENT OFFICE Kohlmarkt 8-10 A-1014 Vienna Facsimile No. 1/53424/535	Authorized officer Hammer e.h. Telephone No. 1/5337058/44

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/HU 94/00039

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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